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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/051,013	10/09/98	BESTOR	T 48075-B-PCT

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EXAMINER	
KERR, J	
ART UNIT	**PAPER NUMBER**
1633	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
09/051,013	Timothy H. Bestor
Examiner	**Group Art Unit**
Janet M. Kerr	1633

☒ Responsive to communication(s) filed on *Apr 10, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-47* is/are pending in the application.

Of the above, claim(s) *2, 3, 5, 13, 14, 17-23, 29, 34-41, and 47* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 4, 6-12, 15, 16, 24-28, 30-33, and 42-46* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicants' response to the restriction requirement, filed on 4/10/00, has been acknowledged. Applicant's election of Group I, claims 1-46, and the election of the following species a) chimeric proteins comprising a zinc three-finger DNA binding polypeptide linked to a CpG-specific DNA methyltransferase polypeptide, b) target genes associated with cancer, c) target genes wherein the target gene is endogenous, and d) animals as the multicellular organism, in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-47 are pending.

Claims 2, 3, 5, 13, 14, 17-23, 29, 34-41, and 47 are withdrawn from consideration as being directed to a non-elected invention (claim 47) or species (claims 2, 3, 5, 13, 14, 17-23, 29, 34-41).

Claims 1, 4, 6-12, 15, 16, 24-28, 30-33, and 42-46 are being examined on the merits to the extent that the claims read on the elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, and 42-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a chimeric protein which comprises a zinc three-finger DNA binding polypeptide linked to a CpG-specific DNA methyltransferase polypeptide, wherein the DNA binding polypeptide binds sufficiently close to a promoter sequence of a target gene, wherein the target gene is an endogenous gene associated with cancer, wherein the promoter sequence contains a methylation site, and wherein the site is specifically methylated such that activity of the promoter, and thus, expression of the target gene is inhibited; vectors comprising a polynucleotide encoding the chimeric protein, cells containing the vector, and pharmaceutical compositions containing the vector.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In this case, the specification does not disclose a chimeric peptide which specifically targets a promoter of an endogenous gene associated with cancer. With regard to genes associated with cancer, the specification discloses that genes that are overexpressed in cancer cells are target genes of the subject invention and include the cancer related genes collagenase 92 kD Type 4, collagenase 72 KD Type 4, osteopontin, calcyclin, fibroblast growth factor, epidermal growth factor, matrilysin and stromolysin. However, the specification does not disclose the sequences of these promoters to which the chimeric protein should bind, or whether the promoter sequences contain a methylation site which is specifically methylated and which results in inhibition of expression of the genes. Similarly, the specification does not disclose the sequence (amino acid or polynucleotide) required in the zinc three finger binding polypeptide which will allow such targeting specificity.

The limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that applicants were in possession of the chimeric proteins or polynucleotides encoding the chimeric proteins which have the claimed targeting specificity, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

Claims 1, 4, 6-12, 15, 16, 24-28, 30-33, and 42-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-10, and 42-46 are directed to a chimeric protein which comprises a zinc three-finger DNA binding polypeptide linked to a CpG-specific DNA methyltransferase polypeptide, wherein the DNA binding polypeptide binds sufficiently close to a promoter sequence of a target gene, wherein the target gene is an endogenous gene associated with cancer, wherein the promoter sequence contains a methylation site, and wherein the site is specifically methylated such that activity of the promoter, and thus, expression of the target gene is inhibited; vectors comprising a polynucleotide encoding the chimeric protein, cells containing the vector, and pharmaceutical compositions containing the vector.

Claims 11, 12, 15, 16, and 24-26 are directed to a method for inhibiting expression of an endogenous target gene associated with cancer in an animal comprising contacting a promoter sequence of the target gene with the chimeric protein to specifically methylate the promoter sequence resulting in inhibition of expression of the target gene.

Claims 17, 28, and 30-33 are directed to a method for inhibiting expression of an endogenous target gene associated with cancer in an animal comprising contacting a promoter sequence of the target gene with the chimeric protein to specifically methylate the promoter sequence resulting in inhibition of expression of the target gene in the animal.

The specification discloses specific methods for selecting zinc finger proteins that bind to predetermined sequences in the HIV-1 5' LTR, and methods of inactivating HIV in cells *in vitro*. However, the specification does not disclose any predetermined sequences in target endogenous genes associated with cancer, or any specific zinc finger DNA binding polypeptide which would selectively bind to the targeted genes such that specific sites on the promoters of the targeted genes are methylated, resulting in inactivation of the promoters and inhibition of gene expression.

The specification only indicates that cancer related genes of interest include collagenase 92 KD Type 4, collagenase 72 KD Type 4, osteopontin, calcyclin, fibroblast growth factor, epidermal growth factor, matrilysin, and stromolysin. However, the specification does not provide any "predetermined sequences" associated with the regions of these promoters such that selection of appropriate zinc finger proteins could be achieved, or whether these particular promoters have specific sites which can be methylated and thereby inactivated such that expression of the gene is inhibited. Moreover, the specification does not provide any amino acid sequence of a chimeric protein or polynucleotide encoding the chimeric protein which has the claim-designated properties. Given the lack of guidance in the specification as to a particular chimeric protein having the claim-designated properties, or methods for specifically making the chimeric protein having the claim-designated properties, one of skill in the art would not be able to make the chimeric protein without undue experimentation.

With regard to using the chimeric protein to methylate specific sites on a promoter, thereby inactivating the promoter and inhibiting expression of the endogenous gene associated with cancer, the specification does not disclose any specific chimeric protein to be used in the method, nor does the specification disclose how to administer the protein, per se. For example, there is no teaching of the amount of chimeric protein to administer, or the site of administration. In addition, there is no teaching in the specification of endocytosis of the protein such that a sufficient amount of protein is incorporated into the cell, transported to the nucleus, and binds to the appropriate target gene. As the specification does not disclose a particular chimeric protein with the claim-designated properties or a method of administering the protein, per se, it would require undue experimentation for one of skill in the art to use the chimeric protein as claimed.

With regard to methods of contacting a promoter with the chimeric protein via a vector comprising a polynucleotide encoding the chimeric protein, the methods encompass gene therapy. However, the specification does provide sufficient guidance in the specification with respect to the amount of vector to administer, the route of administration, the required expression level of

the vector, or the tissue to be targeted such that the chimeric protein is synthesized in the appropriate cell at a sufficient level for binding to the targeted gene, methylating a specific site on the promoter of the gene and inhibiting expression of the gene. Moreover, at the time of filing, the art of gene therapy was known to unpredictable and non-routine. In the "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" (published December 7, 1995), Orkin and Motulsky indicate that clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol; that major difficulties of gene therapy include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host; that it is not always possible to extrapolate directly from animal experiments to human studies; and that while the most straight-forward application of gene therapy may be in the treatment of single-gene inherited disorders, practical difficulties need to be addressed, i.e. delivery of the appropriate gene to a specific cell type or tissue, gaining access to the relevant cell type for correction of the defect, assessing the total fraction of cells in a tissue that need to be corrected, achieving the level of expression required for correction, and regulating expression of the added gene once it is transferred into appropriate target cells (see, e.g., pages 1 and 2, points 2, 3, and 5, for example, page 5, under "Single-gene inherited disorders", and page 14, bullet paragraphs 3-6). Similarly, Verma *et al.* (Nature, 387:239-242, 1997) indicate that "In principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged; problems such as lack of efficient delivery systems, lack of sustained expression, and host immune response reactions remain formidable challenges; although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is no single outcome that we can point to as a success story" (see page 239, under Abstract, and left column, paragraphs 1-2). Note that the obstacles apply to the claim-designated viral vectors, i.e., retroviral, adenoviral, and adeno-associated viral vector delivery systems (see, e.g., pages 240 and 241, under the sections entitled "Retroviral vectors", "Adenoviral vectors", and "Adeno-

associated viral vectors"). Furthermore, Ledley (Pharmaceutical Research, 13:1595-1614, 1996) discloses that while there is growing confidence that gene therapy will provide important pharmaceutical products, and that clinical trials have demonstrated that genes can be introduced into patients by several different methods and will express potentially therapeutic gene products, significant hurdles remain. Several recent clinical studies failed to demonstrate the expected pharmacological effects. Moreover, some of the methods that have been proposed for gene therapy have limiting toxicities, are difficult to manufacture and quality control, or are more costly than current therapies (see page 1595, right column, second paragraph). Retroviral vectors can be directly administered to patients, though the applicability of this approach is limited by the rapid inactivation of retroviruses by human complement (see page 1596, right column, last paragraph bridging page 1597). The major limitation of adeno-associated viruses has been difficulty in developing packaging cell lines that will produce sufficient titers of the virus for clinical use without the presence of helper virus (see, page 1597, right column, lines 1-4). Adenoviral vectors have been demonstrated to be toxic, inducing cytopathic and immunogenic responses *in vivo*. Preclinical and clinical studies have demonstrated that the level and persistence of gene expression using adenoviral vectors may be inhibited by the immunological responses against the adenoviral particle, and inflammation in tissues targeted by the vector (see page 1597, right column, last paragraph). Moreover, Ledley states that the effectiveness of gene delivery *in vivo* is poorly predicted by *in vitro* results. Reasons why *in vitro* results would not be recapitulated *in vivo* include various biological barriers that are not reflected in *in vitro* models, and interactions between DNA or formulated DNA complexes with serum and blood elements (see page 1603, right column).

In view of the lack of guidance in the specification of a particular chimeric protein having the claim-designated properties, the lack of teaching in the specification of how to use the chimeric protein such that the expression of an endogenous target gene associated with cancer can be inhibited via methylation of specific sites on the promoter of the target gene, and the

unpredictability in the art at the time of filing of gene therapy, one of skill in the art would not be able to make the chimeric protein, the vector comprising a polynucleotide encoding the chimeric protein, cells comprising the vector, or pharmaceutical compositions comprising the vector or protein, nor use the chimeric proteins or vectors as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 6-12, 15, 16, 24-28, 30-33, and 42-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered vague and indefinite by the phrases "mutated DNA methyltransferase portion" and "DNA binding protein portion" as it is unclear what type of mutation is intended, and what a "portion" of a protein represents. The metes and bounds of the phrases are unclear.

Claim 6 is confusing because the claim recites "The method of claim 1", however, claim 1 is directed to a chimeric protein, not a method. Clarification is requested. Claim 6 is also rendered vague and indefinite by the phrases "at least a portion of a mutated M.*SSS*I DNA methyltransferase protein" and "at least a portion of a mutated mammalian DNA methyltransferase protein" as it is unclear what mutation is required and which portion of the protein is intended such that the protein has the claim-designated activities. The metes and bounds of the phrases are unclear.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to John LeGuyader, Supervisory Primary Examiner of Art Unit 1633, at (703) 308-0447. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633.

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